Application of classic medicinal chemistry strategies in the rapid generation of novel dipeptidylpeptidase-IV inhibitors

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Abstract

The marketed DPP-IV inhibitors represented by Vildagliptin, Saxagliptin, and Alogliptin trigged the discovery of tens thousands of novel DPP-IV inhibitors. Inspired by the good potency and easily structural modification, we initiated a series of modification of Aloglitpin with classic medicinal chemistry strategies. Herein, we reviewed how we generated diverse and highly potent inhibitors X (IC_{50}= 0.3 nM), Y (IC_{50}= 3.6 nM), Z (IC_{50}= nM), and E (IC_{50}= 1.4 nM) through scaffold hopping triggered optimization, B (IC_{50}= 0.7 nM), C (IC_{50}= 0.4 nM), A (IC_{50}= nM) through pharmacophorehybridization based lead generation, F (IC_{50}= nM) via the extendedcombination of these strategies.In this way, the development of DPP-IV inhibitors will eventually become the classic case in themedicinal chemistry history like COX-2 inhibitors and sulfonamides.

Keyword

DPP-IV inhibitor, medicinal chemistry strategy, scaffold, pharmacophore

1. Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemiacaused by either insulin deficiency or insufficient response to the hormone[1]. According to the International Diabetic Federation (IDF), more than 371 million people were affected by this disease

worldwidein 2012[2]. Its epidemic brings great burden to patients and the social. The disease itself associated with the multi-system complications accounts for substantial proportion of premature mortality and morbidity and cost over 471 billion dollar on its health care last year.Type 2 diabetes (T2D, formerly referred to as non-insulin-dependent or adult-onset diabetes)results from the body's insufficient response to insulin. Although T2D comprises over 90% of diabetes patients, its process is potentially preventable by proper lifestyle alternation and medical treatments. Thus continuous effort has been devoted on the anti-diabetic research and drug development.

Incretin effectis induced by enteric glucose and contributes to more than 70% insulin stimulation[3], which demonstrated to be an feasible mechanism of anti-diabetic research and drug development. Glucose like peptidase-1 (GLP-1) is one of the important incretin hormones which increases insulin secretion and sensitivity, beta cell mass, and satiety, as well as reduces glucagon secretion and gastric emptying[4].Distinctly fromother incretin hormones, GLP-1 reserves glucose regulatory function in T2D patients. However, at normal physical condition, GLP-1 is rapidly cleaved by dipeptidyl peptidase IV (DPP-IV) and lost its function[4].Understanding of GLP-1's inactivation process revealed the role of dipeptidyl peptidase IV (DPP-IV) and contributed to the development of oral bioavailable DPP-IV inhibitors[5].

Herein, we reviewed our structure modifications based on Alogliptin, a DPP-IV inhibitor developed by Takeda pharmaceutical company. By adoption of classic medicinal chemistry strategies, we rapidly generated various novel DPP-IV inhibitors as the lead compounds. Together with further activity or pharmacokinetic properties driven optimization processes, we successfully acquired several DPP-IV inhibitors with either great in vitro biological activity or in vivo efficacy. In this way, we represented a successful and effective flow of rapidcandidate generation with drug like properties based on specific market drugs.

2. Promiscuity of dipeptidyl peptidase-IV and DPP-IV inhibitors

Up to date, several DPP-IV inhibitors have been marketed and become first line therapy in T2D all over the world, represented by Sitagliptin**1**[6], Vildaglipin**2**[7], Saxagliptin**3**[8], Alogliptin**4**[9], Linagliptin**5**[10], Gemigliptin**6**[11], and Teneligliptin**7**[12] (**Fig. 1**). These inhibitors can be divided into peptidomimetics and non-peptidomimetics. Besides Sitagliptin and Gemigliptin, one class of peptidomimetis is pyrrolidineanalogs, which have been widely studied and are represented by

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Vildagliptin andSaxagliptin[13]. As non-peptidomimetics, Alogliptin and Linagliptin were developed based on high-throughput screening and displayed very fine pharmacokinetic and pharmacodynamics profiles[9-10].

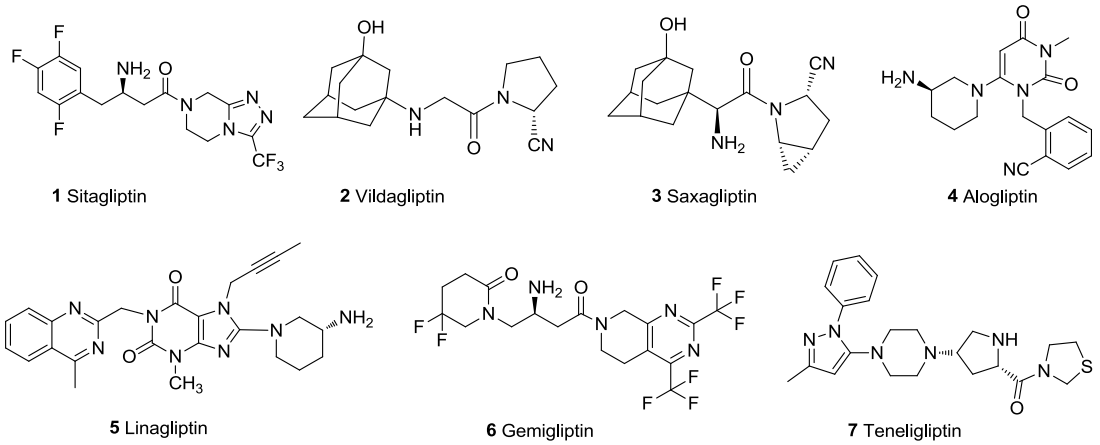

Figure 1. Marketed DPP-IV inhibitors.

These different classes of DPP-IV inhibitors can effectively inhibit DPP-IV enzyme no matter what distinct structures they bear. Thus the DPP-IV enzyme compromises with a great substrate diversity which we referred as promiscuity.The promiscuity provides the room for us to conduct various molecular operations on the market drug. On the other hand, lots of research on DPP-IV enzyme proved this promiscuity. In the crystal, DPP-IV is a dimer. Each subunit consists with an α/β-hydrolase domain and an eight-bladed β-propeller domain with N-terminal located at the same place of the dimer[14]. These two domain formed large cavity as the active catalytic site and binds with the substrate or the inhibitor[15]. The cavity within the subunit consists of three active site.The S-1 site has the catalytic triad (Ser-630, Asp-708 and His-740) which interacts with the substrate at the Ser-630 elbow. The side chains of Tyr-666, Tyr-662, Val-711, Val-656, Trp-659 and Tyr-631 formed the hydrophobic S1 pocket which is responsible for proline specificity of DPP-IV. The crystal structure of human DPP-IV in complex with diprotin A suggested unprotected and protonated N-terminus of the substrate strongly interacts with Glu-205, Glu-206 of S2 pocket[16]. Whereas the S3 pocket formed by Ser-209, Arg-358, and Phe357 is responsible for the DPP-IV selectivity against DPP-8/9[17].These cavitiesallow large diversity and variations of substrate. In another way, this means the modifications on the specific drug have greater chance to acquire candidates with fine drug-like properties. Thus we initiated a systematic modifications on Alogliptinbyclassic medicinal chemistry strategies in order to generate more candidates as potent

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and effective DPP-IV inhibitors.

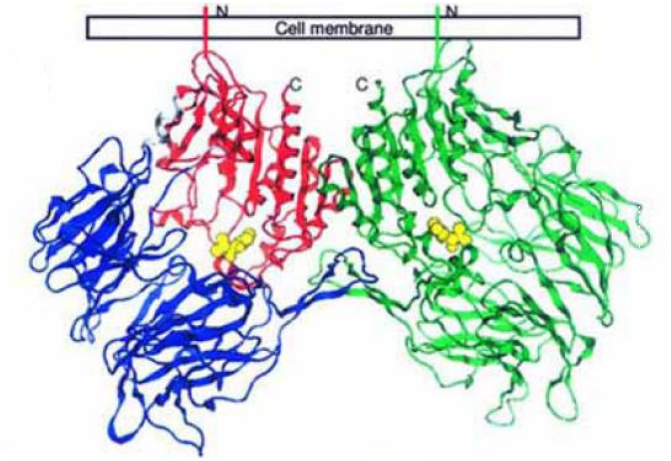

Figure 2. crystal structure of DPP-IV in complex with diprotin A[15] 此图替换或删除.

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3. Scaffold hopping based generation of DPP-IV inhibitors

For target based drug development, most lead compounds confronted attrition fate due to the distance between *in vitro* activity and *in vivo* efficacy. To reduce such attrition rate and to get more compounds with balanced drug like properties, systems biology/pathology/pharmacology[18], fragment based approach[19], and scaffold hopping strategy[20] were developed for the lead discovery. Among them, scaffold hopping has proved itself to be an efficient way to retrieve active compounds avoiding from poor physicochemical and pharmacokinetic properties. Scaffold hopping, initially introduced in 1999 to identify structurally novel compounds with similar biological activities to an know active compounds[20c, 21], has been widely used in lead optimization[22]. Many marketed drugs were derived from other know drugs or natural products[23], indicating that this operation was much early than the term " scaffold hopping". Typical example of scaffold hopping is represented by COX-2 inhibitors refecoxib (Vioxx) and valdecoxib (Bextra) which were separately sold by two pharmaceutical giants with only difference in five-member hetero rings (**Fig. 3a**, **3b**)[24].Another scaffold hopping process could be elucidated between morphine and tramadol (**Fig. 3c**, **3d**)[25]. With quite different 2D structures, these two drugs displayed a similar layout in 3D superposition (**Fig. 3e**). Scaffold hopping by ring opening of morphine led to tramadol with less activity but better pharmacokinetic and toxic profiles. Thus keeping key pharmacophore features conserved, backbone variation could acquire drug-like compounds, even of improved pharmacokinetic (PK) and toxic properties.

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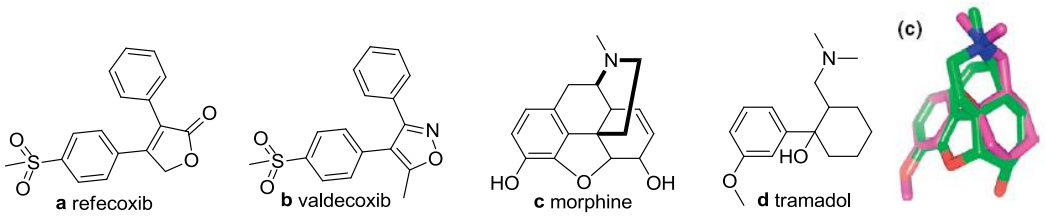


Figure 3. examples of scaffold hopping. (a): refecoxib, (b): valdecoxib (Bextra), (c): morphine, (d): tramadol, (e): superposition of morphine (COLOR) and tramadol (COLOR).许婷婷重新计算

During the discovery process of Alogliptin, its precursor quinazolinone analog indicates the key binding sites: aminopyperidinyl binds Glu-205, Glu-206 with the N-terminus; cyanobenzyl locates in the S-1 pocket; carbonyl binds the Tyr-631 as a hydrogen donor[9]. Thus for our start drug Alogliptin, we first conducted scaffold hopping to search for novel compounds by keeping these key functional groups conserved.Pyrimidoneanlogs were rapidly generated and screed for inhibitory activity (**Fig. 4**, **Tab. 1**) represented bythienopyrimidinecompound **8** (IC_{50}=0.3 nM vs. 3.4 nM that of Alogliptin)[26].Generally this scaffold hopping operation maintained the activity profiles as expected except compound **12**and**13**.12,13 活性下降原因？

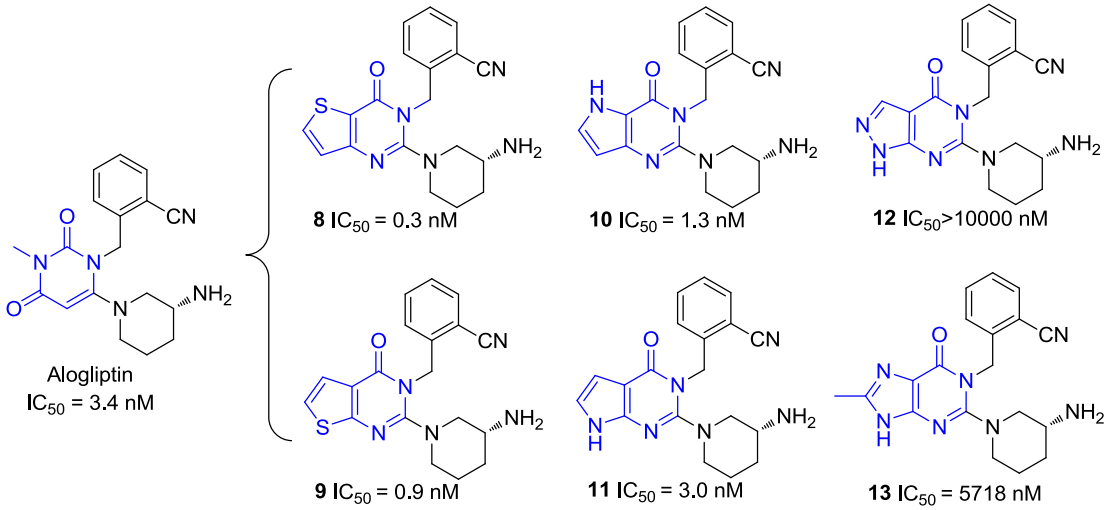
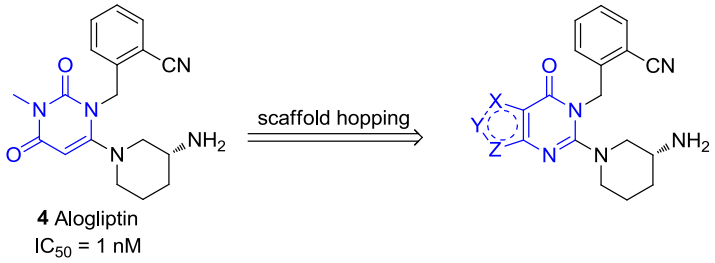


Figure 4. Scaffold hopping from Alogliptin.13 是否有无取代的？

Table 1. inhibitory properties of compound **8**-**13**.



	X	Y	Z	DPP-IV (nM)	DPP-8 (μM)	DPP-9 (μM)
8	S	CH	CH	0.3	>25,000	>25,000
9	CH	CH	S	0.9	>25,000	>25,000
10	NH	CH	CH	1.3	>25,000	>25,000
11	CH	CH	NH	3.0	>25,000	>25,000
12	CH	N	NH	>10,000	>25,000	>25,000
13	N	CCH_3	NH	5718	>25,000	>25,000

Inspired by the scaffold hopping from morphine to tramadol with improved ADME-tox properties, we further launched a PK-driven optimization on compound **8** for its insufficient in vivo glucose lowing efficacy. In this stage, we found the intrinsic metabolic instability within compound **8** and identified thienyl as the soft fragment by in vitro microsomes incubation and metabolite identification (data not shown). Further replacement of thienyl with pyrrolyl significantly increased the metabolic stability, yet reduced oral bioavailability caused by high efflux during the absorptive process (compound **11**). Modifications on pyrrolopyrimidine scaffold eventually gave compound **10a** exhibiting compatible in vitro indicators (IC_{50}=1.3 nM, F=41%) and better in vivo efficacy than those of Alogliptin (**Fig.5**)[27].

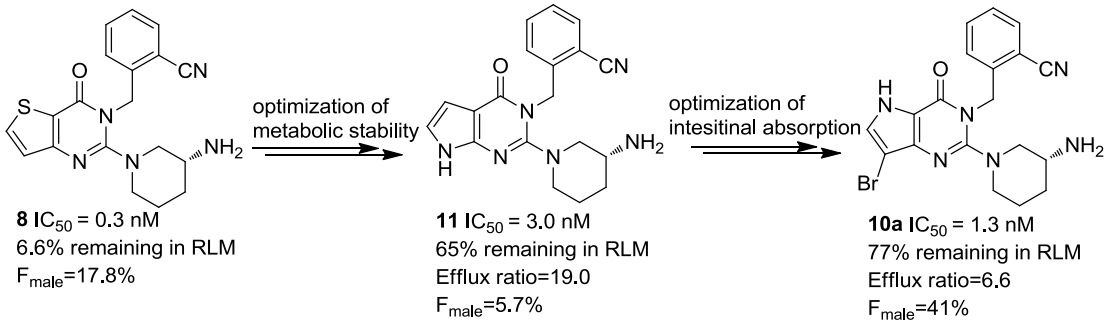


Figure 5. PK- driven optimization on compound **8**.

In the mean time, optimization on other backbones were carried out as well. Although little achievement was obtained, screening on target and by- products derived from compound **12** still gave us confidence for further optimization on scaffold hopping products with losing activity (**Fig. 6**). And the nano molar grade activity of compound **12b** may provide an potential explanation for large decrease in compound **12** and **13**. Large substituents support better accommodation between backbones and the DPP-IV enzyme.待商榷

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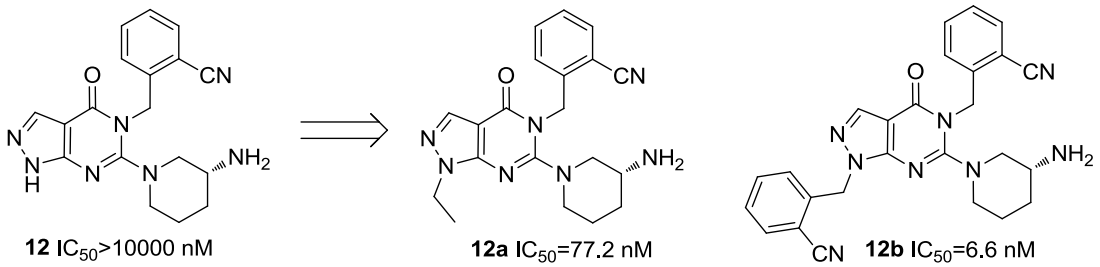

Figure 6. optimization on compound **12**.

4. Pharmacophore hybridization triggered hit-to-lead optimization

With pharmacophores fixed, we rapidly generated two series of pyrimidoneanalogs as potent and oral bioavailable DPP-IV inhibiotrsaccording to pharmacophore-based scaffold hopping. Although key pharmacophore features played a critical role in activity, that didn't mean the pharmacophore must have the exactly same structure. Moreover, the large cavities within DPP-IV protein provided more compatible room for pharmacophore with varied structures. The emerge of Linagliptin well supported this conception. Butynyl of Linagliptin and cyanobenzyl of Alogliptin located in the S-1 pocket in the 3D superposition (**Fig. 7**)[28]. Thus pharmacophorehybridization should also be a potential way to generation DPP-IV inhibitors.

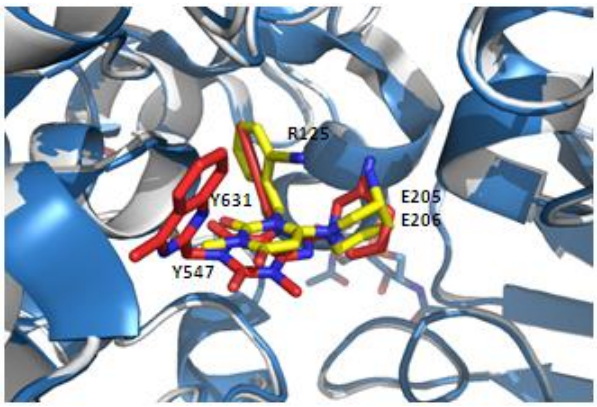

Figure 7. Structure superposition between crystal structures of DPP4 binding Alogliptin(PDB ID. 3G0B, blue and yellow) and Linagliptin (PDB ID. 2RGU, grey and red).

In this part, we first conducted pharmacophore variations directly on pyrimidine dione scaffold of Alogliptin (**Fig. 8**). Hit compound **14** was rapidly synthesized and evaluated with IC_{50} of 198 nM. Due to the previous experience of optimization on compounds obtained from scaffold hopping, we chose compound **14** as the hit compound and initiated a convectional hit-to-lead optimization represented by compound **14a** (IC_{50}=3.1 nM, F=63%, $T_{1/2}$=4.2 h)[28].

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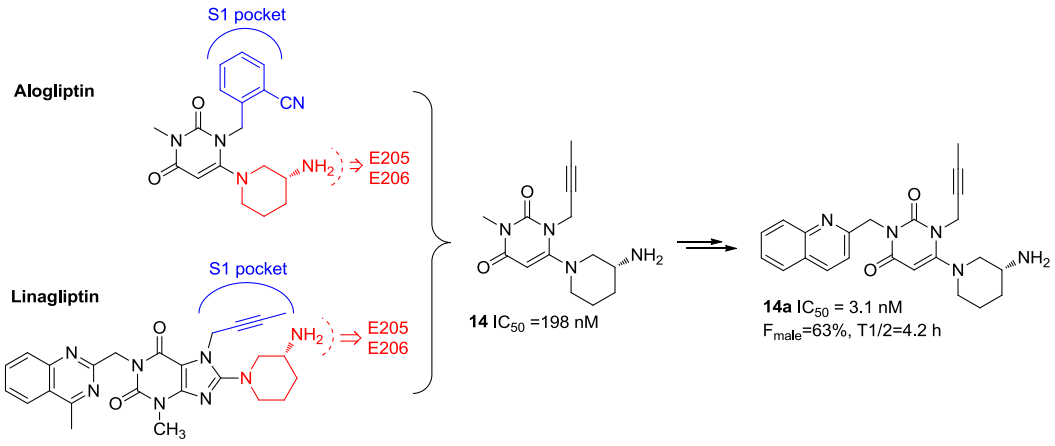


Figure 8. Pharmacophore hybridization on Alogliptin.

Continuous optimization on compound **14a** were mainly focused on quinoline group. Our previous work tried several substituents on different sites of quinoline and lead to compound **14aa** (**Fig. 9**, IC_{50}=0.3 nM, F=73%, $T_{1/2}$=5.0 h)[28].Parallel work of bicyclo-variations were conducted and listed in table 2. Compound **14ai**, substituted by 4-methylquinazolinyl of Linagliptinincreased the activity to 0.7 nM with mild PK profiles compared with compound **14aa**. However , they both demonstrated that pharmacophore hybridization was a feasible way for rapid lead generation of DPP-IV inhibitors.

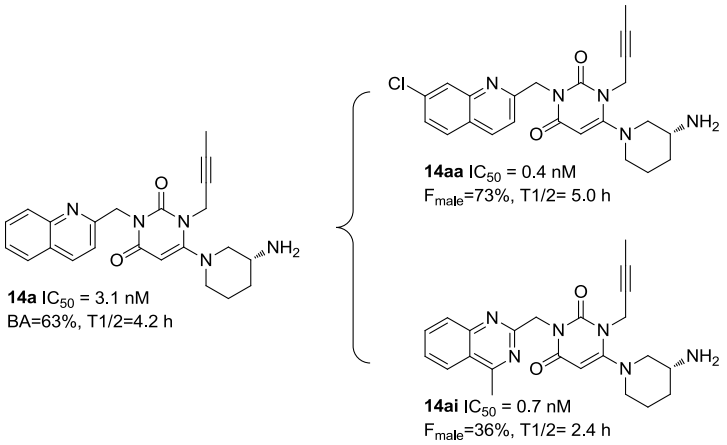
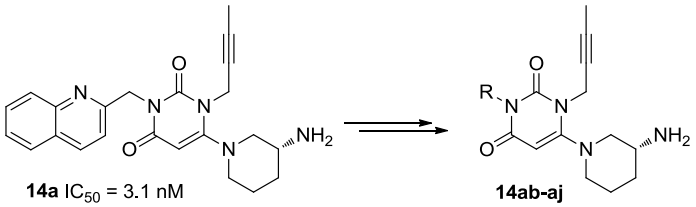


Figure 9.quinoline optimization oncompound**14a**.

Table 2. inhibitory properties of compound **14ab-ai**.



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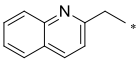
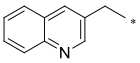
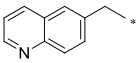
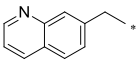
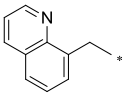
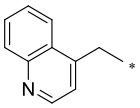
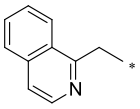
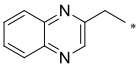
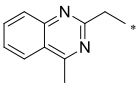
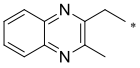
	R	DPP-IV (nM)	DPP-8 (μM)	DPP-9 (μM)
14a		3.1	>100	>100
14ab		12.7	>100	>100
14ac		3.7	>100	>100
14ad		1.3	>100	>100
14ae		21.5	>100	>100
14af		17.3	>100	>100
14ag		17.9	>100	>100
14ah		2.0	>100	>100
14ai		0.7	>100	>100
14aj		2.4	>100	>100

5. Extension of the scaffold hopping and pharmacophore hybridization

Lots of our work was concentrated in Alogliptin and most have achieved promising preclinical candidates. During the above process, we also tried to extend the usage of these molecular operations. Based on our initial scaffold hopping analog **10**, We had butynylhydride and generated hit compound**15**. Moreover, further hybridization of quinazoline of Linagliptin on compound **15**gave compound **15a**(**Fig. 10**, IC_{50}=1.6 nM, F=83%, $T_{1/2}$=4.9 h)[29], as the second pyrrolopyrimidine candidate with much better pharmacokinetic profile than that of Alogliptin and compound **10a**.

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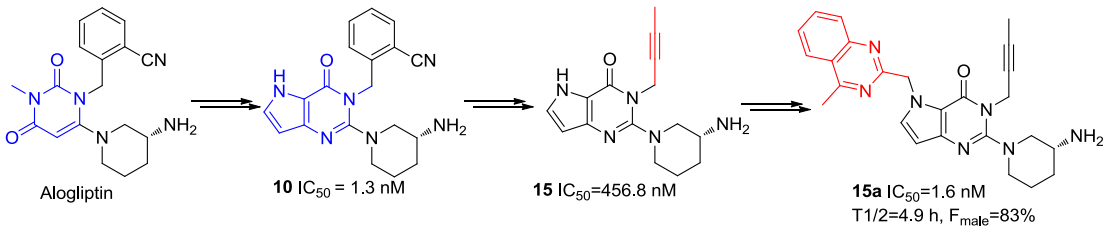

Figure 10. combination of scaffold hopping and pharmacophore hybridization strategies.

Molecular operation on Linagliptin has also tested (**Fig. 11**).Replacement of butynyl of Linagliptin with cyanobenzyl from Alogliptin led to compound **16** (IC50= 5.0 nM). Compound **16** might be a potential compound for further optimization. Yet the incompetence of activity compared to Linagliptin and compounds mentioned above as well as patent consideration paused the following progress. However, this simple reverse pharmacophore hybridization supported that those operation were applicable on other compounds without causing large deviation from know compounds.

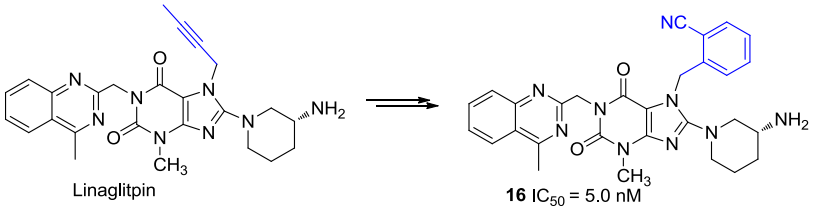

Figure 11.pharmacophore hybridization on other DPP-IV inhibitors.

6. Conclusion 根据前述内容调整

In this paper, we reviewed our medicinal chemistry effort on the market DPP-IV inhibitor Alogliptin and presented several highly potent DPP-IV inhibitors with either better pharmacokinetic profiles or *in vivo* efficacy.The whole process demonstrated the usage of classic medicinal chemistry strategies in efficient generation of DPP-IV inhibitors. Better and deeper knowledge for DPP-IV inhibitor developmentaccumulatedas wider usage of market DPP-IV inhibitors. Andlong-duration DPP-IV inhibitors are also striving their way to the market. The classic and applicable methods introduced here not only are the review of our effort on Alogliptin, but also could be a way to accelerate the development and diversity of DPP-IV inhibitors based on any known molecules.

7. Reference

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